

Evaluation and Management of Patients with Nonerosive Reflux Disease and Esophageal Chest Pain

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The approach to patients with heartburn and noncardiac chest pain is at times confusing. Deciding who should be evaluated by upper endoscopy and determining the first line of treatment may be unclear. This article reviews the pathophysiology, clinical manifestations, and management of 2 of the most common upper gastrointestinal motility disorders, nonerosive reflux disease and esophageal chest pain. These disorders lack the mucosal abnormalities typically associated with gastroesophageal reflux disease (GERD), such as erosive esophagitis, peptic stricture, and Barrett's esophagus. Recent research on the brain-gut axis has provided new insight into the importance of sensory dysfunction in these 2 disorders.

NONEROSIVE REFLUX DISEASE

Approximately 20% of the adult population experiences heartburn on a weekly basis.¹ However, only a fraction of these individuals seek medical attention because of the availability of over-the-counter antacids, histamine₂-receptor antagonists (H₂RAs), and proton pump inhibitors (PPIs), which allows them to self-medicate. Nonerosive reflux disease refers to an entity where individuals complain of heartburn but do not have the endoscopic mucosal complications of erosive esophagitis, peptic stricture, or Barrett's esophagus. Nonerosive reflux disease is the most common subgroup of GERD. Up to 72% of patients who present to general practitioners with heartburn have nonerosive reflux disease.²

Traditionally, GERD has been described as a spectrum of disease, from mild GERD with intermittent heartburn and normal esophageal mucosa to severe GERD with mucosal complications of Barrett's esophagus. However, little clinical data are available to support this disease continuum. Heartburn is equally severe in patients with nonerosive reflux disease and in those with erosive esophagitis.³ Fass and Ofman⁴ have pro-

TAKE HOME POINTS

- Nonerosive reflux disease refers to an entity in which patients have heartburn without endoscopic evidence of erosive esophagitis, peptic stricture, or Barrett's esophagus.
- Esophageal chest pain accounts for approximately 50% of cases of chest pain in the absence of coronary artery disease; the most common cause of esophageal chest pain is acid reflux.
- Many patients with nonerosive reflux disease and esophageal chest pain have a heightened conscious perception of visceral stimuli within the esophagus.
- An empiric trial of acid suppression should be the first line of therapy in patients with heartburn and noncardiac chest pain without alarm symptoms.

posed a new conceptual approach to GERD in which nonerosive reflux disease, erosive esophagitis, and Barrett's esophagus are separate entities with distinct pathophysiologies. Patients tend to remain within these clinical groups over time with little crossover between them. The management goals of nonerosive reflux disease are as follows: (1) identify patients with alarm features who require diagnostic testing, (2) implement an empiric therapeutic trial to improve symptoms, and (3) manage patients in a cost-effective manner.

Pathophysiology

The traditional mechanisms associated with complicated GERD, such as a diminished lower esophageal

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sphincter (LES) pressure and a large hiatal hernia, are uncommon in both nonerosive and erosive reflux disease. However, there is less acid exposure in nonerosive reflux disease compared with erosive esophagitis or Barrett's esophagus.^{5,6} The baseline resting LES pressure is usually normal, and acid reflux tends to occur during transient LES relaxations that are not associated with swallows. Transient LES relaxation is a postprandial phenomenon mediated by the vagal reflex, especially after a fatty meal or during distention of the gastric fundus.

Nonerosive reflux disease is seen in a heterogeneous group of patients. A proposed conceptual model of the brain-gut axis for esophageal functional symptoms has been proposed by Fass (Figure).⁷ Some patients have excessive pathologic acid reflux as the intraesophageal stimuli, while others have normal physiologic acid exposure, suggesting acid hypersensitivity. Visceral hypersensitivity is a heightened conscious perception of visceral stimuli independent of the intensity. Heartburn is perceived and modified by the central nervous system, a complicated process that is being elucidated using esophageal evoked potentials by electroencephalogram, positron emission tomography, functional magnetic resonance imaging, and other methodologies.⁸ Using functional magnetic resonance imaging, Kern et al⁹ have shown that the same intraesophageal acid stimuli activate different areas of the brain in patients with GERD versus normal volunteers. Esophageal symptoms are also modified by peripheral factors such as visceral afferents from other organs that converge at similar spinal cord levels. For example, infusion of fat and acid in the duodenum has been shown to lower the esophageal threshold for heartburn and chest pain.^{10,11} However, the importance of peripheral modification of intraesophageal stimuli is still unclear.

Clinical Manifestations

The symptoms of acid reflux are obvious to health care providers, although patients often describe their symptoms in nonspecific ways. A complaint of epigastric burning may or may not indicate acid reflux. In a prospective study, Carlsson et al¹² utilized a self-administered questionnaire to determine how patients describe their symptoms of GERD and to determine symptom patterns in reflux disease. By describing heartburn as "a burning feeling rising from the stomach or lower chest up towards the neck," the questionnaire had a 92% sensitivity for GERD, using endoscopic erosive esophagitis or positive pH monitoring as the gold standard for diagnosis.¹² This upward motion of burning sensation is a better

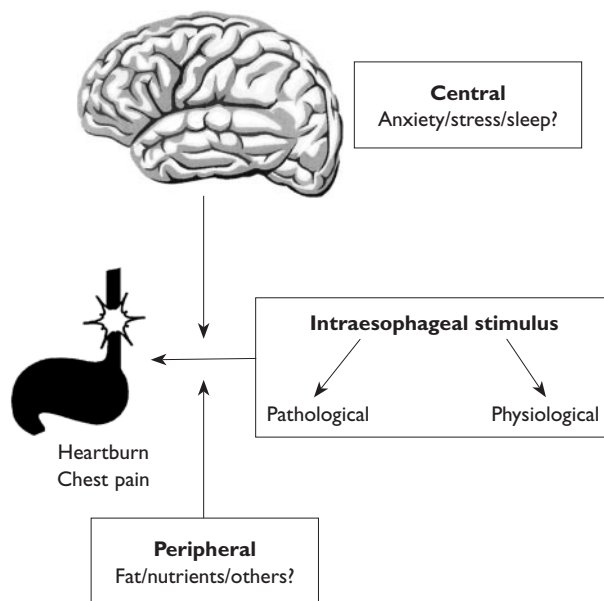


Figure. Proposed conceptual model for the brain-gut axis in nonerosive reflux disease and esophageal chest pain. (Adapted with permission from Fass R. Sensory testing of the esophagus. *J Clin Gastroenterol* 2004;38:631.)

description of acid reflux than stationary epigastric or chest burning.

As with erosive esophagitis, heartburn in nonerosive reflux disease is exacerbated by certain foods and by postural changes. Fatty and spicy foods, coffee (both caffeinated and decaffeinated), and acidic beverages can elicit reflux in some patients. Heartburn in nonerosive reflux disease usually occurs during the day, whereas nocturnal symptoms are more common in patients with erosive esophagitis.⁵ The presence of nocturnal heartburn, regurgitation, and choking are markers for severe GERD associated with low baseline LES pressure and large hiatal hernia.

Although patients with nonerosive esophageal reflux disease have a minimal amount of acid reflux, the heartburn they experience is often severe and refractory to empiric acid suppression, most likely due to visceral acid hypersensitivity.¹³ In a prospective study of patients with alarm symptoms of GERD and in patients with refractory heartburn, women were more likely to have nonerosive reflux disease than men.¹⁴ Coexisting anxiety and depression may be present.¹⁵ General stress and psychologic comorbidities are important in some patients with GERD, especially in those with nonerosive reflux disease. Some patients suffer from general psychological distress rather than a specific psychiatric disorder.

Table 1. Alarm Signs and Symptoms of Gastroesophageal Reflux Disease

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|----------------------------|
| Dysphagia |
| Odynophagia |
| Gastrointestinal bleeding* |
| Weight loss |
| Iron-deficiency anemia |

*Hematemesis, melena, or hematochezia.

Diagnostic Testing

An empiric trial of acid suppression therapy should be implemented first in patients with classic symptoms of heartburn and acid regurgitation. Upper endoscopy does not help direct antireflux therapy as demonstrated in a prospective outcome study.¹⁴ However, the presence of alarm symptoms should alert the physician to the possibility of reflux complications (**Table 1**). The American College of Gastroenterology practice guidelines for GERD recommend diagnostic testing if the patient exhibits alarm symptoms of GERD, is not responsive to therapy, requires continuous chronic maintenance, or has symptoms for a sufficient duration to be at risk for Barrett's esophagus.¹⁶ The risk factors for Barrett's esophagus are based on patient demographics and heartburn duration rather than on heartburn severity (**Table 2**).^{17,18} Endoscopy can improve the management of GERD in 40% of patients with alarm symptoms by dilating esophageal strictures, finding Barrett's esophagus to initiate surveillance, or finding severe esophagitis to indicate the need for chronic maintenance therapy.¹⁴ Radiography with barium swallow using a barium tablet is a reasonable approach to detect stricture in patients with dysphagia, but endoscopy is much more sensitive in detecting mucosa abnormalities.

Ambulatory pH monitoring should be reserved for patients with refractory heartburn that does not resolve despite high-dose PPI therapy. However, up to half of patients with nonerosive reflux disease will have normal total acid exposure in the distal esophagus by pH monitoring.¹⁹⁻²¹ Patients should record their symptoms during pH monitoring to look for a correlation between heartburn and acid reflux, but symptom correlation occurs in only one third of patients with nonerosive reflux disease.²² The Bravo catheter-free pH monitoring system is an alternative that transmits pH data via radio-frequency telemetry to a receiver worn by the patient, avoiding the discomfort of the traditional transnasal pH catheter.²³ The Bravo capsule is placed 6 cm above the gastroesophageal junction to quantify acid reflux in the distal esophagus over a period of 48 hours. Bravo pH

Table 2. Risk Factors for Barrett's Esophagus

| |
|----------------------------|
| Male gender |
| Caucasian race |
| Heartburn duration > 10 yr |
| Age > 50 yr |

telemetry has the potential to improve the detection of abnormal acid reflux and to improve symptom correlation, but the data to support this hypothesis are limited. Patients with heartburn despite normal total acid exposure and negative symptom correlation are described as having functional heartburn by the Rome III criteria for gastrointestinal functional disorders.²⁴ Psychological factors and central sensory disturbance may be more important in patients with functional heartburn than in patients with nonerosive reflux disease.

Treatment

Heartburn traditionally is treated using a stepwise approach to therapy that begins with lifestyle modification and includes use of antacids, H2RAs, and PPIs. However, there are limited data to support this approach based on efficacy and cost, especially when the lower costs of over-the-counter and generic PPIs are considered. A trial of H2RAs in patients with mild and infrequent heartburn is reasonable, but these agents have limited benefit. In a randomized controlled trial involving GERD patients with heartburn, doubling the dose of H2RAs did not provide a greater benefit in patients who did not respond to a single dose.²⁵ PPIs are clearly more efficacious than H2RAs. In a study of patients with nonerosive reflux disease, 24% of those taking cimetidine were asymptomatic after 24 weeks as compared with 60% of those taking omeprazole.²⁶ In patients whose heartburn does not resolve with single-dose PPI therapy, switching to a different PPI can be as effective as doubling the dose.²⁷ Overall, patients with nonerosive reflux disease are less responsive to a PPI than patients with erosive esophagitis. In a review of 7 randomized trials, Dean et al²⁸ found that the symptom response rate for PPIs is only 37% for nonerosive reflux disease as compared with 56% for erosive esophagitis, suggesting that acid hypersensitivity is not resolved by PPI therapy.

Alternative antireflux therapy regimens have been proposed. Over-the-counter omeprazole 20 mg for 14 days is an effective initial regimen in patients complaining of heartburn.²⁹ An on-demand PPI regimen is reasonable in some patients with infrequent heartburn, and computer models have suggested that this

approach can be cost-effective for nonerosive reflux disease.³⁰ Stepwise reduction of therapy should be attempted in patients with heartburn controlled by daily PPI maintenance. In prospective studies by Inadomi et al,^{31,32} stepwise reduction of therapy was successful in 58% of the patients on a single-dose PPI and in 80% on high-dose PPI therapy. Heartburn may improve with treatment for anxiety in individuals with sustained stress, which is correlated with heartburn severity.³³ Relaxation training also has been successful, and esophageal acid exposure was reduced in patients who experienced increasing heartburn during stress events.³⁴

The benefit of antireflux surgery in nonerosive reflux disease has not been clearly demonstrated and remains controversial. Some investigators have reported that the short-term results (ie, symptomatic relief) of laparoscopic fundoplication were similar in patients with and without erosive esophagitis.³⁵ However, in a long-term study with a mean follow-up of 11 years, Spechler et al³⁶ found that 62% of patients who had open fundoplication continued to use antireflux medication on a regular basis. Randomized trials have reported no significant difference in symptom improvement between medical and surgical therapy for GERD.^{36,37} Success of laparoscopic fundoplication highly depends on surgical expertise and patient selection. Postoperative complications are not uncommon and include persistent bloating, dysphagia, diarrhea, and increased flatus.³⁸ We believe fundoplication should be avoided in patients with nonerosive reflux disease, especially in those with acid hypersensitivity, normal or minimal acid reflux by pH monitoring, and psychosocial comorbidity and in those who do not respond to high-dose PPI therapy.

ESOPHAGEAL CHEST PAIN

Chest pain is a common symptom and is often characterized by recurrent episodes of retrosternal chest pain suggestive of myocardial ischemia. Approximately 30% of patients with chest pain have normal coronary arteries by cardiac catheterization. Noncardiac chest pain is a general term used to describe chest pain from other causes in the absence of coronary artery disease. Between 23% and 33% of the general population has noncardiac chest pain,^{1,39} and it accounts for 2% to 5% of all cases presenting to emergency departments.⁴⁰ Patients with noncardiac chest pain are more likely to be treated by a primary care physician and not be referred to specialists.⁴¹ The potential causes of acute and chronic noncardiac chest pain are numerous (**Table 3**). The most common causes are esophageal in origin, accounting for approximately 50% of patients who present with noncardiac pain.⁴² The management goals of esophageal chest

Table 3. Potential Causes of Acute and Chronic Noncardiac Chest Pain

| | |
|------------------|---|
| Gastrointestinal | |
| | Gastroesophageal reflux |
| | Paraesophageal hernia |
| | Achalasia |
| | Hypercontracting esophagus |
| | Pill esophagitis |
| | Esophageal perforation |
| Hematologic | |
| | Acute chest syndrome of sickle cell disease |
| Pulmonary | |
| | Pulmonary emboli |
| | Pneumothorax |
| | Pleural inflammation |
| Vascular | |
| | Thoracic aortic dissection |
| Pericardial | |
| | Pericarditis |
| | Myocarditis |
| Musculoskeletal | |
| | Costochondritis |
| | Muscular pain/strain |
| | Pathologic fractures |
| | Metastasis to chest wall |
| Cutaneous | |
| | Herpes zoster |
| Psychological | |
| | Panic attack |

pain are as follows: (1) identify patients with signs and symptoms to suggest other causes requiring further testing, (2) implement an empiric PPI trial as a diagnostic tool and to improve symptoms, and (3) manage patients in a cost-effective manner.

Pathophysiology

The precise mechanism causing chest pain is poorly understood. The sensation of esophageal chest pain has been attributed to stimulation of chemoreceptors, mechanoreceptors, and possibly thermoreceptors. The conceptual model for the brain-gut axis of esophageal chest pain is the same as that in nonerosive reflux disease (Figure). The amount of esophageal acid exposure is physiologically within normal limits in some patients, suggesting mechanisms of visceral hypersensitivity. Patients with esophageal chest pain have a lower

pain threshold than normal volunteers with intra-esophageal stimuli, such as acid infusion, graded balloon distention, and electrical stimulation.⁴³⁻⁴⁵ Studies with esophageal evoked potentials suggest that pain hypersensitivity results from enhanced afferent transmission and altered cortical processing of the signal.^{45,46}

The most common cause of noncardiac chest pain is GERD, occurring in 40% to 50% of patients. It is unclear why some patients with GERD develop chest pain while others have typical heartburn. The infusion of acid has been shown to lower the esophageal distension threshold for chest pain, implying that pain receptors are sensitized by acid.^{47,48} A hypercontracting esophagus, such as diffuse esophageal spasm, high-amplitude peristaltic contraction (nutcracker esophagus), and hypertensive LES, are found in 10% to 28% of patients with noncardiac chest pain.^{49,50} However, these motility patterns are most likely nonspecific phenomena from external stimuli such as acid reflux rather than the underlying cause for the chest pain. Approximately one third of patients with high-amplitude peristaltic contraction have GERD.⁵¹ Furthermore, nearly half of patients with a hypercontracting esophagus determined by esophageal manometry have normal findings if manometry is repeated.⁵² In some patients, the causes of chest pain may be multifactorial. Coronary artery disease and acid reflux coexist in up to 67% of patients, which further increases the difficulty in differentiating whether pain is esophageal or cardiac in origin.⁵³

Clinical Manifestations

In the emergency department, it is difficult to accurately differentiate cardiac from noncardiac chest pain. Patients may present with squeezing, substernal chest pain radiating to the back, left shoulder, or jaw, mimicking myocardial ischemia. There is a good deal of overlap in chest pain location, intensity, and demographics between cardiac and noncardiac chest pain.⁵⁴ Many patients are admitted because of concern over missing a cardiac event. Comprehensive triage protocols can differentiate between patients at high risk and low risk for myocardial infarction.^{55,56} Acute chest pain associated with respiration, shortness of breath, or cough suggests pulmonary emboli or pleuritis. Severe piercing chest pain with a brachial blood pressure difference of greater than 20 mm Hg between the 2 arms suggests thoracic aortic dissection. Panic attack often presents with acute chest pain and can be identified using a diagnostic model.⁵⁷

Most patients present to the general practitioner or specialist with recurrent or chronic chest pain after cardiac causes are excluded. The presence of heartburn,

regurgitation, dysphagia, or odynophagia should suggest esophageal chest pain. Chest pain occurring at night or exacerbated by eating should suggest the presence of GERD. Achalasia should be considered if the patient has persistent dysphagia. Overall, patients with noncardiac chest pain have a favorable prognosis with very low risk of myocardial infarction and death.^{58,59} However, nearly half of patients continue to have chest pain at least once per month, and many report interruption of daily activities and frequent work absenteeism.^{59,60} Somatization, anxiety, or depression also may be present.⁶¹

Diagnostic Evaluation

Before a diagnosis of esophageal chest pain can be made, cardiac causes must be excluded by a reasonable evaluation. In patients with acute onset of chest pain, pulmonary emboli, pericarditis, and thoracic aortic dissection must also be excluded. In patients with recurrent chest pain, a detailed history and physical examination are needed to identify the underlying cause (Table 3). A diagnostic trial of high-dose PPIs should be the first step in patients with esophageal chest pain and in patients with chest pain of unclear etiology. The effectiveness of the "PPI test" was first demonstrated by Fass et al⁶² in a randomized controlled trial involving patients with noncardiac chest pain that compared a 7-day regimen of high-dose omeprazole (40 mg every morning and 20 mg every evening) with placebo; this test was both sensitive and specific for diagnosing GERD in patients with noncardiac chest pain. Subsequent studies have confirmed this finding. A response to a short course of high-dose PPIs has a sensitivity of 75% to 92% and a specificity of 67% to 90% for identifying GERD, using ambulatory pH monitoring as the gold standard for diagnosis.⁶²⁻⁶⁵ Computer decision analysis models have supported the cost-effectiveness of this strategy.⁶⁶ Starting with a PPI trial can reduce the number of invasive diagnostic procedures by 43% to 59%.^{62,66}

Diagnostic procedures should be reserved for patients who do not respond to the PPI trial. Routine use of upper endoscopy is not recommended because the mucosal complications of GERD are found in only 10% to 25% of patients with noncardiac chest pain.⁶⁷ Upper endoscopy is reasonable if typical heartburn is present and there is an indication for endoscopy (Table 1). Ambulatory esophageal pH monitoring has the highest yield in detecting reflux disease in noncardiac chest pain, as compared with upper endoscopy, esophageal manometry, or provocation testing.⁶⁸ Chest pain episodes should be recorded during pH monitoring to correlate symptoms with acid reflux. Bravo wireless pH telemetry extends the test to 2 days, which

allows patients to report more chest pain episodes and offers greater opportunity for symptom correlation.⁶⁹ Esophageal manometry can be helpful in some patients, especially when ambulatory pH monitoring is not diagnostic. However, analysis of data from a multicenter esophageal manometry database showed that hypercontracting esophageal dysmotility occurs in only 10% of patients with noncardiac chest pain.⁴⁹ Acid reflux is still the most likely underlying cause of noncardiac chest pain, even when manometry is abnormal. Given its low yield, esophageal manometry should not be the initial diagnostic test in patients with noncardiac chest pain unless achalasia is suspected.

Esophageal provocation tests for esophageal chest pain have been well described in the literature. However, their results usually do not direct effective therapy, and the diagnostic yields are lower than ambulatory pH monitoring. The acid perfusion (Bernstein) test is performed by infusing the esophagus with 0.1 N hydrochloric acid versus saline to determine the ability of acid to reproduce chest pain. A positive acid perfusion test is quite specific for GERD-related chest pain (83%–94%), but the sensitivity is less than 40%.⁷⁰ Intravenous bolus of edrophonium, an acetylcholinesterase inhibitor that increases esophageal amplitude and repetitive esophageal contraction, has been used to provoke the patient's usual chest pain. The diagnostic yield of the edrophonium test is between 14% and 30% in patients with noncardiac chest pain,⁷¹⁻⁷³ but the test is also positive in 16% of normal volunteers.⁷³ The sensitivity and specificity of the edrophonium test are unknown because there is no gold standard test for esophageal motility-related chest pain. Stepwise esophageal balloon distension is also used as a provocation test. Patients with esophageal chest pain have a lower distension threshold than normal volunteers.^{74,75} A positive balloon distention test may identify patients with visceral hypersensitivity to distension, but it does not guide therapy.

Treatment

The diagnostic value of a 1- to 2-week course of high-dose PPIs to identify reflux-related chest pain is described above.^{62-65,76} The therapeutic benefit of a longer PPI course has also been documented in randomized controlled trials.^{63,77,78} Improvement is reported in patients with and without abnormal total acid exposure, suggesting acid hypersensitivity with a physiologic amount of reflux.⁶³ A PPI is also effective in patients with hypercontracting dysmotility.⁷⁸ Empiric treatment with a double-dose PPI for 2 to 3 months is a reasonable approach. Medications to relax the hypercontracting esophagus, such as nitrates and calcium

channel blockers, are generally not helpful. Nifedipine and diltiazem were not better than placebo in reducing chest pain in randomized controlled trials.^{79,80} These results are not surprising because abnormal esophagus motility is not the underlying cause of chest pain in most patients.

A few randomized controlled studies have reported the benefit of tricyclic antidepressants and serotonin reuptake inhibitors in noncardiac chest pain at doses lower than those used to treat depression.⁸¹⁻⁸³ Although the mechanism of this benefit is unknown, these agents may produce their effects by impacting the pain and sleep pathways rather than by antidepressant effects. Trazodone can produce global improvement and reduce distress from esophageal symptoms.⁸¹ Treatment of anxiety and panic attack can be effective in patients with noncardiac chest pain and panic disorder.⁸⁴ Cognitive behavioral therapy may be successful in selected patients by improving chest pain episodes, psychological distress, and functional capacity.⁸⁵⁻⁸⁷ This approach includes education, controlled breathing, relaxation training, and diversion of attention from pain.

Potential detrimental treatments should be avoided. Opiate medications should not be used in long-term management. Antireflux surgery is best avoided in patients with esophageal chest pain, especially if symptoms do not improve with PPI therapy and even if acid reflux is documented by pH monitoring. Fundoplication can relieve GERD but may exacerbate visceral hypersensitivity and esophageal distension. The long-term prognosis of patients with noncardiac chest pain is very good, but the quality of life may be poor. Treatment of refractory noncardiac chest pain can be very challenging, especially if a treatable cause is not found or the patient has significant psychosomatic problems.

CONCLUSION

Nonerosive reflux disease and esophageal chest pain are common conditions. Perceived symptoms of heartburn and chest pain are caused by pathologic or physiologic intraesophageal stimuli with visceral hypersensitivity. There is an association between these esophageal disorders and general psychological distress, specifically anxiety and depression. Diagnostic testing is recommended in patients with alarm features of GERD and in patients with signs and symptoms to suggest causes other than the esophagus. An empiric trial of acid suppression therapy should be implemented. In patients with esophageal chest pain or chest pain of unclear etiology, high-dose PPI therapy is a cost-effective diagnostic test. Further evaluation should be reserved for patients unresponsive to PPIs. **HP**

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